Claims 1-14 and 21 were rejected under 35 USC § 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between elements. Applicants respectfully traverse. However, in an effort to expedite prosecution, Applicants have amended claims 1 and 21 to more explicitly describe the claimed methods. Thus, Applicants respectfully request that these rejections be withdrawn.

Claims 1-14 were rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner contends that it is not readily manifest which specific activities (*i.e.*, primer extension, fidelity, chain-terminating nucleotide removal, etc.) of the RT are being examined to ascertain the "level of resistance". Applicants respectfully traverse.

In order to meet the requirements of 35 U.S.C. § 112, second paragraph, the claims must define the patentable subject matter with a reasonable degree of particularity and precision. M.P.E.P. § 2173.02. The primary purpose of this requirement of definiteness of claim language is to ensure that the scope of the claims is clear so the public is informed of the boundaries of what constitutes infringement of the patent. M.P.E.P. § 2173. If the scope of the invention sought to be patented can be determined from the language of the claims with a reasonable degree of certainty, then a rejection under 35 U.S.C. § 112, second paragraph, is not appropriate. See In re Wiggins, 488 F.2d 538, 179 U.S.P.Q. 421 (C.C.P.A. 1973).

Claims 1-14, as amended, describe a broad method for determining the level of resistance not limited to specific activities. The skilled artisan, using the teachings of

the prior art, will easily recognize that various activities may be examined to determine the level of resistance using the methods of the invention. Similarly, one of skill in the art will recognize that the claimed method is not limited by specific types of controls, and the scope of the type of controls that may be used with the claimed method may be determined by the skilled artisan with a reasonable degree of certainty using the teachings of the prior art. The Federal Circuit has decided that the definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of the prior art, and (3) the claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. See, e.g., In re Marosi, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983); Rosemount, Inc. v. Beckman Instruments, Inc., 727 F.2d 1540, 221 U.S.P.Q. 1 (Fed. Cir. 1984); W.L. Gore & Assocs., Inc. v. Garlock, Inc., 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983). Thus, Applicants respectfully request that these rejections be withdrawn.

Claim 14 was rejected under 35 USC § 112, second paragraph, as being confusing for referencing mutations at codon 69 that are insertions. Applicants respectfully traverse. It is well known in the art that one type of mutation is an insertion and that an insertion refers to replacing an amino acid at a codon with more than one amino acid. Thus, no amendment to the claims is necessary and Applicants respectfully request that these rejections be withdrawn.

Rejections under § 103(a)

Claims 1-3, 5-12, 20 and 21 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer et al in view of Ekstrand et al. The Examiner contends that it

would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the detection format described by Ekstrand in the RT assay provided by Meyer, since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription. Applicants respectfully traverse.

There is no dispute that to establish a *prima facie* case of obviousness, the prior art references must provide some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference with a reasonable expectation of success. M.P.E.P. § 2143 (7th ed. 1998). The reasonable expectation of success must be found in the prior art, not in Applicant's disclosure. *See In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Examiner has failed to provide a motivation to combine the references and a reasonable expectation of success. The Examiner, after describing each reference, simple states it would have been *prima facie* obvious to utilize the detection format described by Ekstrand in the RT assay provided by Meyer, since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription. However, the method of Meyer is directed to a totally different approach from Ekstrand. Meyer compares the activity of wild-type RT with mutant RT. Ekstrand, on the other hand, only looks at the amount of RT product as a function of time and RT amount. The Examiner has provided no motivation to combine these very different approaches and no expectation of success.

Additionally, even assuming, *arguendo*, that there is motivation to combine the references and that there is an expectation of success, the method of the instant invention provides several unexpected results. First, as described in the instant specification on pages 12-13, the method of the present invention reproduces cell culture or phenotypic data surprisingly more accurately than previous methods, including the art of record. Additionally, by using detectable dNTP for determining the mechanism of HIV RT inhibitors, not only is it possible to determine the mechanism of action, but one may also identify, at the same time, the dNTP involved in the formation of DEC. Hence, the use of detectable dNTPs unexpected improves the quality and accuracy of the results and provides extra information not suggested by the prior art. Thus, Applicants respectfully request that these rejections be withdrawn.

Claim 4 was rejected 35 U.S.C. § 103(a) as being unpatentable over Meyer et al in view of Ueno et al. The Examiner contends that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize a radiolabeled dNTP, as taught by Ueno, in the assay of Meyer.

For the reasons described above, even assuming, *arguendo*, that there is motivation to combine the references and that there is an expectation of success, the method of the instant invention provides several unexpected results. Thus, Applicants respectfully request that these rejections be withdrawn.

Claims 13 and 14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Meyer et al in view of Ekstrand et al and further in view of Lader. Applicants

respectfully traverse. As described by the Examiner, Larder merely discloses that MNR variants carry mutations at amino acid positions 67, 69, and 70, or an insertion between amino acids 69 and 70. Thus, Larder does nothing to cure the deficiencies described above. Thus, Applicants respectfully request that these rejections be withdrawn.

Claims 1-3, 5-12 20, and 21 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion et al view of Ekstrand et al. The Examiner contends that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to utilize the detection format described by Ekstrand in the RT assay provided by Arion, since this provides a rapid, quantitative, and non-radioactive means for detecting the products of reverse transcription. Applicants respectfully traverse.

Once again, the Examiner has failed to provide a motivation to combine the references and a reasonable expectation of success. However, even assuming, *arguendo*, that there is motivation to combine the references and that there is an expectation of success, as described above, the method of the instant invention provides several unexpected results. The use of detectable dNTPs unexpectedly improves the quality and accuracy of the results and provides extra information not suggested by the prior art. Thus, Applicants respectfully request that these rejections be withdrawn.

Claim 4 was rejected 35 U.S.C. § 103(a) as being unpatentable over Arion et al in view of Ueno et al. The Examiner contends that it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to

utilize a radiolabeled dNTP, as taught by Ueno, in the assay of Arion. Applicants respectfully traverse. For all the reasons discussed above, even if there is motivation to combine the references and there is an expectation of success, the method of the instant invention provides several unexpected results. Thus, Applicants respectfully request that these rejections be withdrawn.

Claims 13 and 14 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Arion et al in view of Ekstrand et al and further in view of Lader. Applicants respectfully traverse. As described by above, Larder merely discloses that MNR variants carry mutations at amino acid positions 67, 69, and 70, or an insertion between amino acids 69 and 70. Thus, Larder does nothing to cure the deficiencies described above. Thus, Applicants respectfully request that these rejections be withdrawn.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: April 12, 2002

By: _____
Anthony C. Tridico
Reg. No. 45,958

APPENDIX TO RESPONSE AND AMENDMENT

IN THE SPECIFICATION

Amendments to 2nd full paragraph of Page 6:

"Extensive genetic analysis of resistant viral isolates generated through *in vivo* or *in vitro* selection has revealed that resistance is generally caused by mutations altering the nucleotide sequence at some specific site(s) of the viral genome. The mutational patterns that have been observed and reported for HIV-1 and that are correlated with drug resistance are very diverse: some antiretroviral agents require only one single genetic change, while others require multiple mutations for resistance to appear. A summary of mutations in the HIV genome correlated with drug resistance has been compiled. See Schinazi, R.F., Larder, B.A. & Meliors, J.W. 1997. Int. Antiviral News. 5, 129-142 (1997). Additionally, an electronic listing with mutations has also become available **on the internet at sites such as hiv-web.lanl.gov or www.viralresistance.com** [at http://hiv-web.lanl.gov or http://www.viralresistance.com]. Of course, as antiretroviral drugs are administered for longer periods of time, mostly in combination with each other, and as new antiretrovirals are being developed and added to the present drugs, new resistance-correlated genetic variants are being discovered. Of particular import is that the combination of antiretroviral agents can influence resistance characteristics."

IN THE CLAIMS

1 . (Amended) A method for determining the level of resistance of HIV to an HIV RT inhibitor comprising:

a) providing a reaction well comprising

at least one template for an HIV RT enzyme,

at least one primer,

at least one detectable dNTP substrate,

at least one HIV RT inhibitor,

at least one ribonucleotide chosen from ATP and GTP or at least one pyrophosphate;

b) adding to the reaction well an HIV RT enzyme chosen from a wild-type RT enzyme **[**or a mutant RT enzyme**]**, wherein said HIV RT enzyme incorporates the **at least one** detectable dNTP substrate or the at least one HIV RT inhibitor into said template;

c) determining RT activity by measuring the amount of the detectable dNTP substrate incorporated into the template;

d) repeating steps b) and c) replacing the wild-type RT enzyme with a mutant RT enzyme

e) determining the level of resistance of HIV to the HIV RT inhibitor **[**using**]** **by comparing** the RT activity **of the wild-type RT enzyme with the RT activity of the mutant RT enzyme.**

21. (Amended) A method for rapid screening the effects of mutations on HIV resistance to an HIV RT inhibitor comprising:

a) providing an array of reaction wells, each reaction well comprising:

at least one template for an HIV RT enzyme,

at least one primer,

at least one detectable dNTP substrate,

at least one HIV RT inhibitor, and

at least one ribonucleotide chosen from ATP or GTP or at least one pyrophosphate;

b) adding to each reaction well a different HIV RT enzyme chosen from a wild-type RT enzyme or a mutant RT enzyme, wherein said HIV RT enzyme incorporates the at least one detectable dNTP substrate or the at least one HIV RT inhibitor into said template **and wherein at least one wild-type RT enzyme is added to at least one reaction well**;

c) determining RT activity in each reaction well by measuring the amount of the detectable dNTP substrate incorporated into the template; and

d) determining the effect of mutations on HIV resistance to the HIV RT inhibitor **[**using step c**]** **by comparing the RT activity of at least one wild-type RT enzyme with the RT activity of at least one mutant RT enzyme**.